

REMARKS/ARGUMENTS

Claims 1-14 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of any one of JP 11099192 (JP '192), DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). The claims have not been amended. Reconsideration is respectfully requested.

The present invention is directed to a composition comprising a radiopharmaceutical metal complex in a container that has a silica coating on the inner surface. The present invention also relates to non-radioactive, preferably lyophilized kits for the preparation of such radiopharmaceutical metal complexes, where the kit composition is supplied in a container that has a silica coating on the inner surface.

Crane discloses a method of using a metal complex and its analogs to diagnose or radioimage breast tumors. Crane only provides a vague reference to the use of a vial to hold its compounds. More importantly, Crane does not even disclose, teach, or suggest using any type of coating on the inner surface of the vial.

JP '192 discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method) are useful to prevent adsorption of radiopharmaceutical products such as a thallium chloride, (^{201}Tl), solution to the surface of the glass of the vial. The Examiner (last paragraph on page 3) states that:

"...JP '192 discloses a composition comprising a stabilizer suitable for a metal complex (eg. chloride) in a container that has a silica coating on the inside."

Applicants suggest that this is a mischaracterization of JP '192. JP '192 refers to ²⁰¹Tl chloride. The chemical species is thus Tl^+Cl^- , which is an ionic species that would be fully ionised in aqueous solution. Ionic species are not "metal complexes". Metal complexes are in the field of coordination chemistry where an organic ligand binds to the metal *via* a covalent bond. There is therefore no correlation between the metal complexes of the present invention and the thallous chloride teaching of JP '192. Consequently, it is erroneous to refer to the chloride ion of JP '192 as a "stabiliser suitable for a metal complex". Metal complexes are an essential feature of the present claims, and Applicants respectfully request that the Examiner withdraw the previous characterization of JP '192 and confirm that JP '192 teaches only ionic species, not metal complexes. Applicants contend that the person skilled in the art would be well aware of these important differences in chemical constitution, and this in fact provides a further reason why there would be considerable doubt over whether the teaching of JP '192 could be applied successfully to radiopharmaceutical metal complexes.

Schott Glaswerke discloses that glass containers having an internal coating of SiO_2 , prepared by a plasma chemical vapour deposition process, are useful for the storage of pharmaceutical or diagnostic solutions. However, Schott Glaswerke provides no further description of a contained material such as radiopharmaceutical metal complexes, let alone a radiopharmaceutical, other than the generic reference to 'pharmaceutical'.

Walther discloses a glass tube with an oxide coating. Walther notes that the prior art taught a silica-coated tube for use with (generic) pharmaceuticals. However, Walther contains no reference to radiopharmaceutical metal complexes per se.

In the Examiner's Appeal Brief Answer ("Answer") dated November 29, 2005, on page 5, line 13, the Examiner sets forth the motivations of using combined prior art references to determine the obviousness of using silica coated vials in radiopharmaceutical metal complexes. The Examiner states "The motivation comes from the secondary references, which teach that coating the inner surface of vials for various pharmaceuticals, including radiopharmaceuticals, provides various advantages." In this respect, Applicants point out that only JP '192 specifically teaches radiopharmaceuticals – Schott and Walther are silent on such agents. Furthermore, there are several other vial coatings that could be used by Crane instead of silica.

For example, silanizing containers to give clear silicone coatings have been used to prevent aqueous pharmaceuticals from adhering to the inner container walls. Furthermore, inorganic titanium/zirconium oxide coatings have been used in glass bottles to prevent pharmaceuticals and beverages from adhering to the inner walls of the bottle. Also, coatings of silicon, boron, zirconium or titanium nitrides have been used to treat the inner surface wall of a quartz, glass, or ceramic container. Containers internally coated with silicone used in the manufacture of lyophilized pharmaceutical products have been used as well. It is important to note here that Crane teaches extensively about its kits and vials being lyophilized, wherein lyophilization aids useful in the preparation of diagnostic kits are useful also for the

preparation of radiopharmaceuticals, Column 5, line 22 to Column 8, line 23. It is also known in the art that the coating inside the surface of a glass container with a silicone material substantially eliminates manufacturing problems and product deficiencies. These examples demonstrate that the person skilled in the art, without knowledge of the present invention, even if presumed to be motivated to improve Crane by the use of a coated vial, would have been faced with a wide range of possible coatings. Hence, even assuming that the person skilled in the art was motivated to improve Crane, the selection and direction of the improvement is far from clear in the absence of hindsight, and could arguably lead towards any of the aforementioned coatings instead of silica.

In light of the aforementioned, Applicants note that the law has long established that "[a] basic mandate inherent in 35 U.S.C. §103 is that "a piecemeal reconstruction of prior art patents in light of the applicants' disclosure" shall not be the basis for a holding of obviousness." *In re Kamm and Young*, 452 F.2d 1052. (C.C.P.A. 1972). Therefore, it would not have been obvious to one skilled in the art to modify the compositions disclosed by Crane (i.e., Tc-99m-ligand complex radiopharmaceutical diagnostic agents) to use vials having a silica-coating inner surface when there are several other various vial coatings that provide 'various advantages' for various pharmaceuticals as well.

Applicants also submit that the present invention describes at length how radiopharmaceutical metal complexes suffer from unforeseen or variable problems that are solved using silica-coated vials. See page 4, line 17 to page 9, line 23 of the present specification. It is very important to recognise that these are not simply adsorption of

radioactivity, but also include eg. particulates and/or precipitates of unknown origin in the radiopharmaceutical liquid. Applying a prior art technology which is directed at solving solely adsorption problems would not therefore be an adequate solution for the person skilled in the art, and could not be expected to solve such diverse problems – again absent knowledge of the present invention. None of these problems, which are specific to radiopharmaceutical metal complexes, were recognized in either JP '192, Schott Glaswerke, or Walther, and hence the cited references simply cannot provide a motivation to apply silica-coated vials to radiopharmaceutical metal complexes. The solution to the problem provided by the present claims is believed non-obvious for this reason.

The Examiner questions why Applicants argued over terminology and asserts that the previous use of the term 'silicon' meant "silicon containing, eg. silicon dioxide or silica" or was a shorthand for "oxides of silicon". Applicants respectfully raised this point for clarification, and point out that this "shorthand" is not an accepted abbreviation in the field – in fact the term 'silicon' has long been used for the chemical element silicon (only), and hence this "shorthand" contradicts chemical nomenclature. When the Examiner fails to define what new abbreviations are being adopted, Applicants are disadvantaged in trying to argue their case. Without the use of precise or conventional terminology, Applicants cannot be sure whether the Examiner's words are to be given their literal/conventional chemical meaning or not. Since Applicants have silica as an essential feature of their claims, it is clearly of vital importance to establish which terms the Examiner recognizes as interchangeable and which not. The prior examples cited earlier on silicone (synthetic polymers) makes it even more important that accurate terminology is applied.

Additionally, the Examiner questions why silica coatings preventing adsorption would not be expected to hold true for metal complexes. As noted above, Applicant's first response to this is that the radiopharmaceutical metal complexes suffer from a range of problems, not just adsorption, and the problem should not be oversimplified or forced to be the same as that of JP '192. Secondly, while metal complexes can exhibit adsorption, the fact is that JP '192 refers to ionic species only. The full translation of the JP '192 document at paragraphs [0013] to [0015] describes the mechanism of adsorption as an equilibrium process involving free potassium ions (K^+) in solution in a glass container as well as the similarity of the monovalent cations Tl^+ and K^+ leading to competition between the Tl^+ and K^+ for the potassium ion binding sites on the glass container. The silica coating of JP '192 is expected [0015] to prevent dissolution of potassium ions from the glass into solution. Since (as argued above), metal complexes are very different species compared to the monovalent cations, Tl^+ or K^+ , the person skilled in the art could not expect any adsorption of metal complexes to occur *via* the mechanism described by JP '192. Therefore there is a serious question mark over whether the solution to the problem taught by JP '192 (ie. preventing leaching of potassium ions from the glass into solution) would be regarded as relevant for metal complexes.

Furthermore, Applicants respectfully present that one 'could' combine references is not the standard for making a *prima facie* case of obviousness as such a standard would only grant patentability to combinations which 'could not' be made. Indeed, if the Examiner's logic were followed, then all radiopharmaceuticals would be provided in silica-coated vials, once the cited prior art in question had published, and no one would contemplate using

uncoated vials let alone any other type of coated vial that has been previously discussed. Accordingly, Applicants respectfully disagree with the Examiner's basis for finding a motivation to combine Crane with any one of JP '192, Schott Glaswerke, or Walther.

Additionally, on page 5, line 12 of the Examiner's Answer, the Examiner states "The primary reference of Crane need not state that their invention needs improvement to be used as a primary reference and to be modified. It is only required that the art as a whole provide the motivation." Crane specifically teaches "solubilization aids" as an essential feature to solve the adsorption problems described therein:

Column 2 lines 33-47 and 56-57,
Column 3 lines 23-33 and 46-47,
Column 7 lines 1-26.

If JP '192, Schott Glaswerke, or Walther were to be combined with Crane in the manner suggested by the Examiner, the 'solubilization aids' taught by Crane would be rendered unnecessary, since the coated vial would (presumably) solve the adsorption problem. This contradicts the teaching of Crane, in that the absence of the 'solubilization aid' would remove an essential teaching of Crane. Accordingly, combining Crane with JP '192, Schott Glaswerke, or Walther in this manner is an invalid combination.

It is important for Applicants to emphasize the point that if Crane were to be combined with JP '192, one would obtain a solubilizer from Crane, and a coated vial and a radiopharmaceutical metal complex from JP '192. As previously stated, the 'solubilization aid' or the solubilizer used to solve the adsorption problem is an essential feature of Crane.

The present invention, however, uses silica-coated vials to solve the adsorption problem. Therefore, in order to solve the adsorption problem with using a coated vial, Crane must present an additional step of removing the solubilizer. Crane, however, does not teach, suggest, or disclose any additional steps to remove the solubilizer. Therefore, absent the present invention, a person skilled in art would not know that silica-coated vials would obviate the need for a solubilizer as taught by Crane. Accordingly, combining Crane with JP '192 in this manner is further evidence of an invalid combination.

Furthermore, Applicants respectfully submit that any such combination would teach away from the present invention. 'Teaching away' simply means teaching a solution that would not lead to the claimed subject matter. As noted by the Federal Circuit:

A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. (emphasis added).

Para-Ordnance Mfg. v. SGS Importers Int'l, 73 F.3d 1085 (Fed. Cir. 1995).

Applicants respectfully submit that the mere fact that a reference may suggest an 'improvement' does not dictate that the improvement will direct one to all other 'improvements'. That is, one improvement can teach away from another, as the two improvements may diverge from each other in their teachings. The *Para-Ordnance* decision (above) clearly states that teaching away does not require a negative teaching in the prior art, the prior art need only teach other, divergent, solutions to be deemed to teach away from an invention

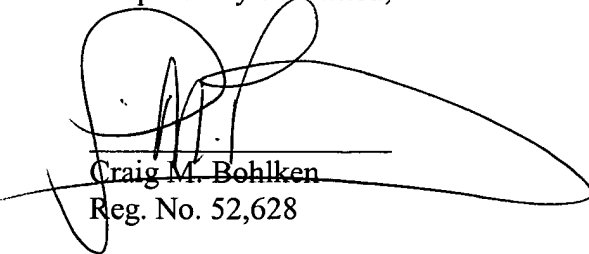
Applicants respectfully submit that it would not have been obvious to one of ordinary skill in the art to use silica-coated vials for containing the radiopharmaceuticals disclosed in Crane. As previously set forth, there are several other vial coating alternatives that could have been used in Crane.

In view of the remarks hereinabove, Applicants respectfully submit that the instant application, including claims 1-14, is in condition for allowance. Favorable action thereon is respectfully requested.

Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

Authorization is hereby given to charge any additional fees which may be due in connection with this communication to Deposit Account No. 502-665.

Respectfully submitted,



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